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Review

Bridging the gap between the randomised clinical trial world and the real world by combination of population-based registry and electronic health record data: A case study in haemato-oncology

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Abstract Randomised clinical trials (RCTs) are considered the basis of evidence-based medicine. It is recognised more and more that application of RCT results in daily practice of clinical decision-making is limited because the RCT world does not correspond with the clinical real world. Recent strategies aiming at substitution of RCT databases by improved population-based registries (PBRs) or by improved electronic health record (EHR) systems to provide significant data for clinical science are discussed. A novel approach exemplified by the HemoBase haemato-oncology project is presented. In this approach, a PBR is combined with an advanced EHR, providing high-quality data for observational studies and support of best practice development. This PBR + EHR approach opens a perspective on randomised registry trials.

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1. Introduction

Clinical science contributes to evidence-based medicine (EBM) being considered the basis for medical decision-making, which in individual cases can be fine-tuned by shared decision-making. EBM justifies the superiority and effectiveness of the provided health care [1]. Over the years, the original idea of EBM was narrowed down to evidence supplied by randomised clinical trials (RCTs). However, a well-known problem in daily clinical practice is the gap between the RCT data and facts and the individual patient features representing the real world of medicine. Specifically, patients' age and the complexities of comorbidities are increasing, making it more and more difficult to justify clinical decisions based on RCT outcomes.

An approach in solving this problem is to expand the RCT world. Common obstacles are inconsistent or unspecific signs and symptoms, low incidence, variable disease phases and precursor lesions, heterogeneity in comorbidity and socioeconomic status, high costs of an RCT and so on. Owing to these practical factors, complicated by ethical aspects, the possibilities of an RCT world expansion are limited.

With respect to these shortcomings of EBM and RCT, much attention has recently been drawn to the potential contribution of cancer registries (CRs) or population-based registries (PBRs) [2]. In this article, we review several aspects of RCT, CR, PBR and electronic health records (EHRs). Subsequently, we will discuss the perspective of merging PBR and EHR as a potentially powerful tool for clinical research. HemoBase, a domain-specific PBR/EHR in haemato-oncology in Friesland, a province in the northern part of the Netherlands, is proposed as a paradigm.

2. Randomised clinical trials, cancer and population-based registries

2.1. RCT

RCTs are the most powerful instruments to investigate the evidence of new therapies while eliminating selection bias and confounding by carefully selecting patients and using strict methodology. RCTs are focused on a specific research question, with a well-defined hypothesis to be tested, and all the types of data necessary to answer the question(s) are collected in a predefined manner, using electronic case report forms. However, the results are often not representative of the real-world patients with comorbidities and/or advanced age, making the RCT knowledge less valuable or in need of extrapolation before it can be applied to clinical practice. A meta-study by Cherubini *et al.* [3] showed that more than 40% of the trials have an upper age limit. Furthermore, in more than 90%, the presence of at least one comorbidity may already lead to exclusion of the patient. In the real world of medicine, most of the patients are older and have more than one comorbidity.

This dilemma is framed as the inferential gap: clinicians are required to fill in where they lack knowledge or where no knowledge yet exists [4,5]. Especially when treating the elderly, the inferential gap may be large.

2.2. CR and PBR

CRs and PBRs have their roots in public health rather than in clinical medicine. Already at the beginning of the 20th century, regional- or domain-(tumour) specific observational registries were started to gain insight into cancer epidemics and risk or environmental factors [6]. The successes of the observational approaches, for example, determination of the etiological roles of smoking, hypertension or infected water are well known. From the 1940s onwards and especially into the 1970s, this resulted in an increase in developing CRs and PBRs.

The design of a CR or PBR is not based on a rigid scientific methodology as RCT design is. Basically, data on new patients and some specific outcomes distributed in time and geographic locus are collected. The SEER database is a well-known example [7,8]. Past decades have shown a tendency to broaden the purposes in domain or scope of the registry. In addition, from the 1990s onward, momentum has risen, linking regional databases to national databases, and national databases to international databases. These developments have increased the power of observational research. A serious drawback is still the immense efforts needed to achieve high-quality data, such as in standardisation, reclassification or adjudication of critical data.

Especially in Europe, many regional- or domain-specific CRs were developed. In sum, approximately 160 CRs and PBRs are active [9,10]. Well-known registries in haemato-oncology, for example, had their start-up in Burgundy (France), South Netherlands, Sweden, England and Scotland [11–15]. The expansion of CRs and PBRs resulted in national and international cooperative projects such as the Belgian and Netherlands Cancer Registry (NCR) and projects such as the European Network of Cancer Registries (ENCRs), Eurocare-5 and Eurocourse [6,9,12,16]. A common denominator in the evolution of CRs and PBRs is that they started as quantitative registries of basic data regarding incidence, prevalence and overall survival. Subsequently, processes developed for adding qualitative data of tumour characteristics and patient care. Linkage of CRs and PBRs resulted in large observational databases with potential power to address clinically relevant research questions [10,17]. An interesting possibility is the precise linking of PBR data with RCT data to address specific questions. Recently, this was published for Hodgkin's lymphoma in a paper that addressed the potential difference between the real world and the RCT world [18]. Another